

REMARKS

Claims 1, 5-7, 11-15, 18-21, 23-26, 27, 29, 33, 35-37, 42-44, 48-52, 54-56, 60, and 65 are pending. Claims 2-4, 8-10, 16-17, 22, 28, 30-32, 34, 38-41, 45-47, 53, and 57-59, 61-64 are cancelled.

Claims 1, 5-7, 11, 13, 15, 18-21, 23, 26-27, 29, 33, 35-37, 42-44, 48, 50, 52, 56, 60, and 65 are currently amended. Support for these amendments is found throughout the specification, for example in the claims as well as paragraphs [0020]-[0023], [0027]-[0029], [0054]-[0058], [0071]-[0075], and [0101]-[0108] of the specification. None of these amendments adds new matter.

Applicants reserve the right to file one or more divisional applications directed to any cancelled or non-elected subject matter and claiming priority to the present application.

Rejections under 35 U.S.C. § 112 1st ¶ - Enablement Requirement

Claims 33-61 and 65 are rejected for lack of enablement. Although the Examiner acknowledges that “the specification has exemplified a composition comprising attenuated *Salmonella typhimurium* vector displaying anti-CEA antibody to target CEA antigen expressed on colon cancer cells (see Example 1, 2), the Examiner alleges that the specification is not enabling for methods for treatment of neoplasia with a composition for delivering a therapeutic agent to a target cell comprising microorganism expressing a cell surface exogenous molecule that binds to an antigen of a target cell.

In reply, applicants traverse the rejection. The claimed invention is directed to a composition for delivering an agent to a neoplastic cell of a solid tumor expressing a neoplasm-specific antigen. The composition comprises an agent and an attenuated *Salmonella* microorganism that has an antibody or fragment thereof on its cell surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor. The claimed invention is also directed to methods of treating neoplasia in a subject via administering a

therapeutic composition of the attenuated *Salmonella* microorganism described above, in the absence or presence of the agent.

Use of Attenuated Salmonella is Enabled

The first issue raised by the Examiner is enablement of administering any microorganism in the treatment of neoplasia. Without conceding the correctness of the Examiner's position, the claims have been amended and are now directed to administering an attenuated *Salmonella* microorganism.

Applicants note that the Examiner acknowledged that "the specification has exemplified a composition comprising attenuated *Salmonella typhimurium* vector displaying anti-CEA antibody to target CEA antigen expressed on colon cancer cells (see Example 1, 2)," (see page 17 of May 18, 2007 Office Action, 13th line). Applying Jain et al. 2001 (Expert Opin. Biol. Ther. 1(2):291-300) and Pálffy et al. 2006 (Gene Therapy 13: 101-105), applicants submit that use of bacteria expressing an exogenous nucleic acid was considered to be known in the art. Jain et al. state that "there is a reluctance to use unmodified pathogenic bacteria for therapeutic purposes. However, considerable information is available about bacteria that makes their genetic manipulation a practical and safe approach." (p. 292 1st column, 3rd paragraph). Further, Pálffy et al. report that "bacteria-mediated transfer of plasmid DNA into mammalian cells (bactofection) is a potent approach to express plasmid-encoded heterologous proteins (protein antigens, hormones, toxins, or enzymes) in a large set of different cell types including phagocytic and non-phagocytic mammalian cells" (page 101, 2nd column 1st paragraph) and "to reduce the risk of clinically symptomatic infections to minimum, the bacteria are genetically modified" (page 101, 2nd column, 2nd paragraph). Pálffy et al. also state that "plasmids in bacterial vectors carry antigens that are expressed in the eukaryotic cells after transfection. Attenuated bacteria can also express the antigens themselves without a transfer of DNA into the eukaryotic cells and in addition they act as adjuvants." (page 104, 1st column, 2nd paragraph). The Examiner noted that "Pálffy et al. support earlier studies to use bacteria that are attenuated." The state of art at the time would have enabled a skilled artisan to make and use an attenuated *Salmonella* microorganism expressing a molecule of interest without undue experimentation.

Moreover, the application in this case discloses how to make and use the attenuated *Salmonella* compositions of the invention. For example, the specification provides guidance and description via several examples on how to clone a gene, such as CEA (Examples 1 and 2), construct a recombinant *Salmonella* vector displaying protein product of the cloned gene at the organism's cell surface (Example 2), determine expression of the cloned gene (Examples 1 and 2), and how to use the microorganism's surface antibody that binds to a neoplastic-specific antigen of a neoplastic cell, such as CEA, in a method for treatment of neoplasia (Example 3). The examples and description of how to express CEA at the surface of *Salmonella* provides methodology useful for the cloning and expression of other known neoplastic-specific antibodies or fragments thereof that bind to a neoplasm-specific antigen. Applicants point out that claim 33 has been amended to recite an "attenuated *Salmonella* microorganism," which is supported by paragraphs [0027] and Examples 1-2 in the specification in addition to claim 45. Thus, the instant specification in combination with the state of the art provides the skilled artisan reasonable guidance on how to make and use the claimed *Salmonella* composition for a skilled artisan would have been able to make and use an attenuated *Salmonella* microorganism with a reasonable expectation of success.

Claimed Composition Can Be Delivered At Efficacious Levels

The Examiner raises a second issue concerning the therapeutic efficacy of the claimed invention when delivered to humans in that it is allegedly exemplified only as a hypothesis in the application. While Example 3 in the application is prophetic, the law states that examples are not required and an applicant's invention does not have to be actually reduced to practice prior to filing. *See In re Stephens*, 529 F.2d 1343, 1345 (CCPA 1976) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366-67 (Fed. Cir. 1997) (working examples in the specification are not necessarily required to comply with the enablement requirement); *See also Pfaff v. Wells Elecs*, 525 US 55 (1998) ("there is no requirement that an invention be reduced to practice before being patented"). A description of an actual reduction to practice is not the only way by which to satisfy the written description requirement- a constructive reduction to practice is also an established method of disclosure. *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 926

(Fed. Cir. 2004). Thus, there is no legal requirement that the instant specification include working examples.

Furthermore, a reduction to practice under the patent law does not require human testing in actual use circumstances for a period of time but rather only a reasonable showing that the invention will work to overcome the problem it addresses. *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994). The FDA is responsible for overseeing the testing of safety and efficacy of therapeutic compositions; such demands are not within the confines of the USPTO. See *In re Watson*, 517 F.2d 465, 476 (CCPA 1975). Thus, an applicant is not required to demonstrate that a therapeutic composition is effective and safe for human consumption. See *In re Sichert*, 566 F.2d 1154, 1160 (CCPA 1977).

Applying Gura et al. 1997 (Science 278: 1041-1042), Kelland et al 2004 (Eur J Cancer 40:827-836) and Kerbel et al 2003 (Cancer Biology and Therapy 2 (supp 4): S134-139), applicants submit that a mouse model (a transgenic or nude mouse resulting in tumor formation) is routinely used as a model for the human condition and results in mice that can and are extrapolated to humans. Toso et al. report that “a strain of *Salmonella typhimurium* (VNP20009), attenuated by chromosomal deletion of the purI and msbB genes, was found to target to tumor and inhibit tumor growth in mice [which]... led to the... phase I study of the intravenous infusion of VNP20009 to patients with metastatic cancer.” (Toso et al., (2002) *J Clin Oncol.* 20(1):142-52). Furthermore, applicants assert that use of a human CEA transgenic mouse model as described in the application [see Example 3] is preferred practice in the art rather than a xenograft mouse model as suggested by the Examiner. For example, in Gura et al., who teach how to maximize screening systems so that biological information that has been accumulated can be used to identify anti-cancer compounds (Gura et al. (1997) *Science* 278: 1041-1042), state that the xenograft model is not optimal to use: “Xenograft models miss effective drugs. The animals apparently do not handle the drugs exactly the way the human body does” (Gura et al. (1997) *Science* 278: 1041-1042; page 1041, first column, 3rd paragraph). This contradicts the examiner’s comments on page 8 of the May 18th office action (4th sentence from bottom): “Kelland et al. emphasize that this model is valuable in cancer drug development.” In addition, Kelland et al. state that “the use of xenografts is relatively time-consuming and expensive, raises

animal ethical issues and there are instances where the model is inappropriate as a likely predictor of clinical outcome,” (abstract; Kelland et al., (2004) *Eur J Cancer* 40:827-836). Finally, Kerbel et al. recognize that “a shift has occurred towards developing and using spontaneous mouse tumors arising in transgenic and/or knockout mice engineered to recapitulate various genetic alterations thought to be causative of specific types of respective human cancers,” (abstract; Kerbel et al., (2003) *Cancer Biology and Therapy* 2 (supp 4): S134-139)). Therefore, the state of the art at the time of the invention and the discussion herein demonstrate that results obtained using tumorigenic mouse models can be extrapolated to a subject suffering from a cancer.

Applicants contend that the art at the time of filing was well-established for gene delivery. For example, Medina and Guzman discuss the use of bacterial vectors for gene delivery. (Medina and Guzman (2001) *Vaccine* 19:1573-80). In their review, Medina and Guzman state that “microorganisms which have the capacity to access the cytoplasm of infected cells, such as *Shigella* and *Listeria*, have been used to deliver DNA constructs in which the expression of the recombinant antigen was under the control of a eukaryotic promoter.” (page 1576, 1st column, 1st paragraph; Medina and Guzman (2001) *Vaccine* 19:1573-80). Furthermore, the authors conclude that “use of live bacterial carriers constitutes a powerful tool to achieve an efficient delivery of either vaccine antigens or DNA vaccine constructs” (page 1578, 1st column, 1st paragraph; Medina and Guzman (2001) *Vaccine* 19:1573-80). Thus, the specification in combination with the state of the art at the time of the invention would have enabled a skilled artisan to make and use the *Salmonella* compositions claimed without undue experimentation.

Gene-Silencing Cassette is Enabled

As a third issue, the Examiner expresses concern regarding the use of a microorganism expressing a gene-silencing cassette. Applicants proffer references to rebut the Examiner’s allegations that attenuating or inhibiting expression of a target gene in a cell by a dsRNA is unpredictable. Caplen et al. state that “double stranded RNA has been shown to induce post-transcriptional gene silencing (PTGS) in a number of species including nematodes, planaria, trypanosomes, hydra, zebrafish, Drosophila and mouse.” (Caplen et al., (2000) *Gene* 252: 95-

105; p. 95, 2nd column). Caplen et al. further point out work carried out by others in the art where “in vivo PTGS and RNAi need only be induced locally in a small number of cells to generate gene silencing throughout the organism” and “pre-incubation of dsRNA in whole cell lysates significantly potentiated its capacity to inhibit specific gene expression” (Caplen et al., (2000) *Gene* 252: 95-105; p. 103, 2nd column, 2nd paragraph). Thus, gene-silencing had been practiced with reasonable success by skilled artisans at the time of filing.

Furthermore, applicants show below that the Examiner acknowledges that introduction of dsRNA which is targeted to a specific gene may result in the attenuation/inhibition of the targeting genes (See page 11 of May 18, 2007 Office Action, 13th line). In addition, Pálffy et al. state that “genetic information for specific dsRNA production can be delivered into the target cells via bactofection.” (Pálffy et al. (2006) *Gene Therapy* 13:101-105; page 104, 1st column, 2nd paragraph). Although the examiner notes that “a major obstacle to therapeutic gene silencing is the delivery problem – the necessity of introducing short dsRNAs into specific organisms,” “emerging evidence suggests that this obstacle might be surmountable” [text found directly after statement cited by the examiner from the post-filing reference Novina et al.,(2004) *Nature* 430: 161-164; page 164, 2nd column, 2nd paragraph]. Further, Novina et al. discuss that “RNAi promises to be one of the most useful laboratory tools yet” (Novina et al., page 164; 1st column, 2nd paragraph) and the “use of chemically synthesized siRNAs has... helped to define gene function in vertebrate cells, and has even been extended to human cells *in vitro*” (page 164; 2nd column, 2nd paragraph). In addition, another post-filing reference cited by the Examiner (Paroo et al., (2004) 22(8): 390-394) states that “siRNA has gained greater acceptance in two years than traditional antisense oligonucleotides achieved in twenty because it is relatively easy for non-specialists to apply the technique successfully.” (page 390, 2nd column, 1st paragraph) and “by the time siRNA appeared, a wide variety of efficient delivery systems for nucleic acids had been developed and were commercially available.” (Paroo et al., page 390, 2nd column, 2nd paragraph). These references show that a person of ordinary skill in the art would have understood that delivery of dsRNA was routine and would not require a person of ordinary skill in the art to engage in undue experimentation because the availability of commercial delivery systems would enable the skilled artisan to routinely screen various nucleic acid concentrations in various cell

types using the well-established transfection/infection methods practiced in the art. Therefore, the specification in combination with the state of the art provides reasonable guidance on how to express and deliver a gene-silencing cassette using the *Salmonella* compositions of the invention with a reasonable expectation of success.

Salmonella Expressing An Antibody Is Enabled

The Examiner expresses concern that any protein, molecule, or antibody would be functional and thus capable of binding to a target cell expressing an antigen in a method for treating neoplasia. Applicants have amended claims 33 and 65 to reflect an antibody or fragment thereof that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor, thereby obviating this rejection. Applicants note that commercial antibodies directed to the antigens recited in claim 54 were known and available at the time of filing (for example, the Cak1 antibody (Cancer Res. 1992 Jan 1;52(1):181-6) or the Cdk4 antibody (Mol Vis. 2002 Feb 8;8:17-25)). Thus, one of ordinary skill in the art would have had such amino acid sequences available to them or would have been able to determine the peptide sequences responsible for antigen binding using methods established in the art. On page 17 (May 18, 2007 Office Action) in the ninth sentence from the top, the Examiner stated: “Based upon the prior art, there is expected to be structure or peptide sequence variation that is capable to bind to an antigen.” Thus, the art at time of filing in combination with the technology would have guided the skilled artisan to make the claimed *Salmonella* microorganism expressing an antibody or fragment thereof that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor without undue experimentation and with a reasonable expectation of success and subsequently use the composition in a method for treating neoplasia.

Administration of Attenuated Salmonella is Enabled

The Examiner’s fifth issue concerns treating a tumor by administering the claimed composition by any route. Applying McCluskie et al. 1999 (Mol Med 5:287-300), applicants contend that the art at the time of filing provided the skilled artisan sufficient guidance to administer the compositions to elicit a pharmacological response. McCluskie et al. state that the “route of administration of plasmid DNA vaccines influences the strength and nature of immune

responses in mice and non-human primates. Optimal dose and immunization schedule will most likely vary between species." (abstract). This remark suggests that it is routine procedure for a person of ordinary skill in the art to determine the administration route and dose for the delivery of a therapeutic composition in order to elicit a desired response in a subject. Thus, a researcher would not be unduly unburdened to engage in this routine experimentation.

Furthermore, as discussed above, Toso et al. report that an attenuated strain of *Salmonella typhimurium* (VNP20009) was "found to target to tumor and inhibit tumor growth in mice [which]... led to the... phase I study of the intravenous infusion of VNP20009 to patients with metastatic cancer" (Toso et al., (2002) *J Clin Oncol.* 20(1):142-52). Therefore, the art at the time of filing guides the skilled artisan as to the route of administration to elicit a desired pharmacological response.

In view of the foregoing, applicants maintain that a person of ordinary skill in the art would know how to use the *Salmonella* compositions of the instant invention given the state of the art at the time of filing combined with the specification. Any further experimentation would require routine testing guided by the specification, and the amount of experimentation to make and use the invention is not undue and is permissible. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejections under 35 U.S.C. § 112 1st ¶ - Written Description

Claims 1-29, 33-61, and 65 are rejected for failing to comply with the written description requirement. The Examiner alleges that the claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time of the application was filed, had possession of the claimed invention."

In reply, applicants traverse the rejection. As acknowledged by the Examiner, applicants were in possession of an exemplary embodiment of invention for the specification exemplified a

composition comprising attenuated *Salmonella Typhimurium* vector displaying anti-CEA antibody to target CEA antigen expressed on colon cancer cells (Examples 1 and 2). Applicants have amended claims 1, 33 and 65 to reflect a *Salmonella* microorganism that has on its surface an antibody or fragment thereof that binds to a neoplasm-specific antigen on the surface of a neoplastic cell of a solid tumor. FIGS. 4-5 of the specification specifically demonstrate that applicants were in possession of a CEA antibody-expressing *Salmonella* microorganism that binds to CEA antigen. As discussed above, applicants note that commercial antibodies directed to the antigens recited in claim 54 were known and available at the time of filing (for example, the HER-2 antibody, the Cak1 antibody (Cancer Res. 1992 Jan 1;52(1):181-6) or the Cdk4 antibody (Mol Vis. 2002 Feb 8;8:17-25)). Thus, one of ordinary skill in the art could identify the antigen to which the antibody was directed to using established methods practiced by the skilled artisan at the time of filing and deduce the antigen peptide sequence that binds to the antibody. Such sequences could then be incorporated into the attenuated *Salmonella* microorganism of the invention via recombinant molecular biology techniques practiced by the skilled artisan. According to the court in *Noelle v. Lederman*, the written description requirement would be met since the functional characteristics of the antigens (see those listed in claim 54) were sufficiently known as antibodies directed to such antigens were commercially available. *See Noelle v. Lederman*, 355 F.3d 1343 ,1349 (Fed. Cir. 2004). Thus, one skilled in the art would reasonably believe that applicants had possession of the claimed invention at the time of filing.

In view of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw this ground of rejection

Rejections under 35 U.S.C. §102

The Examiner alleges that Claims 1-27 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Bereta et al. 2002 (Cancer Res 43: abstract 3288, page 663).

In reply, applicants traverse the rejection and submit that the Bereta et al. reference is not prior art as to the claimed invention. To rebut a rejection under 35 U.S.C. 102(a), “applicants are to provide a satisfactory showing that would lead to a reasonable conclusion that [applicant] is

the inventor of the subject matter disclosed in the article and claimed in the application.” *In re Katz*, 687 F.2d 450, 455, 215 USPQ 14, 18 (CCPA 1982). Pursuant to 37 C.F.R. §1.132, applicants submit herewith a Declaration of the named inventors establishing that the Bereta et al. reference is the applicants’ own work that comprises the subject matter of the rejected claims. Applicants state that the 2002 reference consists of their own work wherein recognition of their contribution to the abstract presented at the American Association for Cancer Research Meeting is duly noted in the line of authors (Michel Bereta is cited as the first author and Howard Kaufman is cited as the last, senior author).

In view of the attached Declaration, Bereta et al. should be removed as prior art as to the claimed invention.

The Examiner alleges that claims 1-4, 6-7, 9-11, 25-27, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Francisco et al. 1993 (PNAS, 90(22): 1044-8) since the reference teaches “a composition comprising a functional ScFv antibody fragment attached to the outer surface of *E. coli* that is capable to bind an antigen with high affinity that also comprises a construct comprising a chloramphenicol-resistance gene.” Applicants respectfully disagree with the Examiner and traverse the rejection for the reference teaches a method for expressing and screening antibody fragments on the surface of *E. coli* (a virulent microorganism) for the in vitro production and selection of useful antibody fragments (see Abstract, page 10444). Francisco et al. do not teach a composition comprising an attenuated *Salmonella* microorganism that expresses an antibody or fragment thereof on its surface that binds to a neoplasm-specific antigen on the surface of a neoplastic cell and a therapeutic agent. Therefore, Francisco et al. does not anticipate the claimed invention.

In view of the foregoing, Applicants request that the Examiner reconsider and withdraw these grounds of rejection.

Double Patenting Rejection

The examiner alleges that claims 1-29, 33-61, and 65 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-29, 33-61, and 65 of co-pending

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Application No. 11/213499 (US patent publication no. 20060083716). Applicants note that claims 2-4, 8-10, 16-17, 22, 28, 30-32, 34, 38-41, 45-47, 53, 57-59, and 61-64 of the instant application are cancelled. Claims 1, 5-7, 11, 13, 15, 18-21, 23, 26-27, 29, 33, 35-37, 42-44, 48, 50, 52, 56, 60, and 65 are currently amended. Thus, the pending claims in the present application do not claim the same invention as that of the '499 application. In view of the foregoing, Applicants request that the Examiner reconsider and withdraw this ground of rejection.

The Commissioner is authorized to charge any fees that might be due to Deposit Account No. 08-0219.

Respectfully submitted,

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